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AdvaMed
Advanced Medical Technology Association

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

RE: Docket #01D-0489 - "Guidance for Clinical Trial Sponsors On the Establishment and Operation of Clinical Trial Data Monitoring Committees"

Dear Madam/Sir:

AdvaMed is pleased to provide comments on the draft guidance document, "Guidance for Clinical Trial Sponsors On the Establishment and Operation of Clinical Trial Data Monitoring Committees (DMC)." AdvaMed, the Advanced Medical Technology Association, (formerly the Health Industry Manufacturers Association) represents more than 800 innovators and manufacturers of medical devices, diagnostic products and medical information systems. Our members produce nearly 90 percent of the $68 billion health care technology products consumed annually in the United States, and nearly 50 percent of $159 billion purchased around the world annually.

AdvaMed's comments are the following:

General Comments:

As innovators and manufacturers of medical technology, AdvaMed member companies sponsor clinical research and therefore understand the importance of maintaining the safety of trial participants and the scientific integrity in clinical research studies. While AdvaMed supports the ***appropriate*** use of DMCs, we believe that the sponsor should have the authority to decide when a DMC is necessary. Therefore, AdvaMed recommends that FDA clearly state that the use of a DMC is voluntary only and not binding for clinical trial design or trial conduct and thus, not enforceable. The document serves as a point of reference on the operation of DMCs with no implied or direct regulatory requirement that sponsors adopt the recommendations.

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Moreover, AdvaMed is concerned that the guidance is too prescriptive regarding when and how a DMC functions. FDA already requires periodic clinical updates on the progress of a clinical trial and requires almost immediate reporting of serious events (unanticipated adverse events). Therefore, a requirement that a sponsor establish a DMC represents a redundant review of the clinical trial to a third party while still maintaining the current reporting requirements. This redundancy will add significant cost and complexity to the conduct of many medical device trials. In many cases, a DMC will not add significant value, and furthermore, could add confusion, increase the number of points of information exchange, and thus undermine the purpose of having such a reviewing body.

Document Scope
The scope of this guidance document covers drugs, biologics, and device trials. In fact, the guidance often assumes that all trials, including device trials, are blinded. For many device trials, blinded studies are not possible. Unfortunately, FDA fails to distinguish between drug and device trials. Furthermore, FDA does not differentiate between public-sponsored studies, such as National Institutes of Health (NIH) studies, that require the use of DMCs and industry-sponsored studies that do not. AdvaMed suggests that the guidance de-emphasize the notion of "one size fits all" and provide more flexibility to meet various circumstances and objectives under which studies are designed and conducted. AdvaMed strongly recommends that FDA either modify the document, specifying any specific information or sections applicable to each product segment (device, drug, or biologic), or consider drafting a separate document for device trials.

Specific Comments:

Section 1. Introduction and Background

AdvaMed recommends that FDA either condense this section into a brief summary or include it as part of the preamble to the document.

Section 1.1. History of DMCs

FDA should recognize the other terms currently being used and accepted by FDA such as "Data Safety Monitoring Board". Moving forward, if FDA intends to introduce DMC as the new terminology, then it should indicate this in the background information.

Section 1.2. Current Status

FDA states in the last sentence of this section "...that the discussion of advantages and disadvantages of various approaches to DMC operation is relevant to all trials, regardless of the sector of the sponsor." This sentence seems to indicate that a DMC is required for all trials. AdvaMed recommends that FDA clarify that a discussion of

the various DMC approaches should occur only when the need for a DMC has been determined.

Section 2. Determining the need for a DMC

In the first paragraph of section 2, FDA states that "...DMCs have generally been established for large, randomized multisite studies that evaluate interventions intended to prolong life or reduce risk of a major adverse health outcome...". Further, FDA suggests that "...a DMC is not needed or advised for every clinical study." However, subsequent paragraphs and other sections in this guidance suggest otherwise. Based on the current language in the document, even low risk studies such as those for in vitro diagnostics (IVDs) may require a DMC. IVD studies, as a general rule, should never require the use of a DMC. Again, AdvaMed recommends that FDA modify the language to clarify that the use of a DMC is voluntary and that the trial sponsor makes the final determination to use one.

Circumstances in which FDA recommends the use of a DMC are so extensive that they include the majority of controlled trials that are conducted for product approvals. If this guidance document is accepted as written, many device trials will unnecessarily require DMCs. Throughout the document, FDA describes various situations for which it recommends the use of a DMC. These circumstances include:

- High risk to patient (section 2.1)
- Long term trials (section 2.2)
- Trials affected by external and/or internal changes (section 2.3)
- Studies where interim analyses are planned (section 2.3, 4.41, 6.3, 6.6 and 7.2)
- Phase I and early Phase II studies (section 4.4.2)
- For expedited regulatory review (section 5.2)

Most clinical studies conducted by device manufacturers will fall into one or more of the above-listed categories. This has not been the "typical" use of DMCs for device trials. AdvaMed acknowledges the need for a DMC in high risk/long term studies, or studies where the sponsor and FDA agree that a DMC would facilitate expedited regulatory review. However, sponsors should not be forced to use DMCs just because of concerns for bias, scientific validity and interim analyses. Sponsors must design trials to ensure scientific validity, whether a DMC is used or not. Furthermore, in industry-sponsored studies, FDA plays the significant role in reviewing scientific validity and merit of the trial before the trial begins and during the conduct of the trial. Establishing a DMC would create unnecessary duplication of efforts. AdvaMed again urges the agency to emphasize in the document that the trial sponsor makes the final decision regarding the need to use a DMC.

To assist the sponsor in determining whether a DMC is practical for a given trial design, it is recommended that the guidance document include a decision tree flow chart that would provide guidance to a sponsor on the appropriate need for a DMC for a particular study design, size, and duration.

Section 3. DMCs and Other Oversight Groups

Information in this section seems like background and overview information as it describes the role of existing committees and oversight bodies such as Institutional Review Boards (IRBs). AdvaMed recommends that FDA move this information to Section 1. Introduction and Background.

Section 4. DMC Establishment and Operation

In this section, FDA's description of a DMC is the typical DMC model used in NIH sponsored trials. Objectives of clinical trials for industry-sponsored trials may not be the same as those for public-sponsored trials. Thus, the role and operations of DMC must be flexible to meet the sponsor's needs. Selection of DMC members, responsibilities and operational structure must reflect the objectives that sponsors have in conducting clinical trials.

NIH trials are generally research and science oriented studies, while industry-sponsored trials are primarily for the development of a product with the goal of obtaining product approval from the regulatory agency. In the industry-sponsored studies, FDA shares a vital role (together with the sponsor) in assuring proper conduct and scientific validity of the study. Thus, DMCs in industry-sponsored studies have limited responsibilities compared to those in NIH-sponsored studies. In this section, FDA's definition of the role of the DMC is too prescriptive; AdvaMed recommends that FDA modify this description to ensure greater flexibility for industry sponsors to establish a DMC that accounts for the shared responsibility that already exists between the sponsor and the agency.

Section 4.1. Committee Composition

AdvaMed agrees that the trial sponsor selects and appoints the DMC members.

Section 4.2. Confidentiality of Interim Data and Analyses

This section of the document emphasizes the need to deny the sponsors access to interim data and the results of interim analysis. In the case of device trials, blinding of data to the sponsor may be more problematic than for drug trials given that the adverse event description will often reveal possible issues with the device or interim trial results. Since the sponsor has access to adverse event information during the

course of the trial, this represents a contradiction. AdvaMed recommends that FDA address this potential conflict regarding blinded data and trial designs for devices.

Section 4.3. Establishing Standard Operating Procedures

While the principle of having a guiding framework in which the DMC and sponsor operate is appropriate, AdvaMed believes that it is not necessary to have Standard Operating Procedures (SOPs) that would be submitted to FDA in advance of trial initiation. Alternatively, when preparing a DMC agreement, the sponsor could define procedural matters and processes in the agreement rather than establishing written and approved SOP's that could possibly delay the initiation of the trial. Furthermore, it would not be necessary to submit this agreement to FDA for review since this represents an agreement between the DMC and sponsor as it would not fall within the scope of current clinical trial regulations.

Section 4.4. Potential DMC Responsibilities

Section 4.4.1.2. Monitoring for Safety

The guidance mentions cases in which the DMC would advise stopping the study when the sponsor becomes aware of adverse events. AdvaMed also recommends that the document include a reference to the opposite case in which a DMC, with a broader overview of the study and the needs of the patient population, might advise that the risk/benefit for the patient population would suggest that the study should continue.

Section 4.4.1.3. Monitoring Study Conduct

In addition to reviewing primary and secondary endpoint data, the DMC may review data related to the administration of the trial and protocol compliance. However, this type of administrative data could detract from the clinical data that the DMC is chartered to review and potentially could be misinterpreted by the DMC. For example, rates of ineligibility, dropouts, and protocol violations may not be valuable when viewed merely as numbers and could be taken out of context by the DMC. If a protocol violation is defined as any deviation from the protocol, no matter how minor the variation, then it may be difficult for the DMC to ascertain the meaning behind a rate of protocol violations. Also, upon reviewing information on the rates of completeness and timeliness of data, the DMC again could get a false impression that there is a safety issue when there may be simply a training issue on how to complete the forms.

Section 4.4.2. Early Studies

AdvaMed disagrees with the concept that a DMC would be useful in an early study, especially when the investigator or product manufacturer is the IDE sponsor, and is subject to " potentially strong influences related to financial and/or intellectual incentives". A DMC may not be the appropriate oversight mechanism for these studies. Conflicts of interest could be effectively addressed by the proper relationship between the sponsor and the IRB's or by a conflict of interest committee or official.

Also, for device trials, the Center for Devices and Radiological Health has encouraged sponsors to first conduct pilot or feasibility studies. At this stage of the investigation, the sponsor should be very close to the data to understand safety and effectiveness outcomes in real time and should not be prevented from reviewing it. Pilot studies generally do not carry enough patient numbers to provide statistical significance, and are thus less sensitive to interim "looks" at the data. Results from pilot studies eventually lead to the design of the pivotal study, in which fewer "surprises" may be expected and a look at interim data may not be needed unless the interim analysis was prospectively built into the trial design. In any case, a DMC would not add value, and could again unnecessarily add complexity and confusion to the study.

Section 4.4.3.2. Maintaining Meeting Records

In order for the DMC to carry out its charter of independent review of clinical trial safety, the meeting minutes documented by the DMC should not be made available to the regulatory agency either during or at the end of the trial. To submit such information to regulatory agencies would undermine the independence and integrity of the DMC to act in the best interest of the patients and the medical community by providing the regulatory agencies with the opportunity to question the recommendations made by the DMC. Without the ability to carry out its charter the value of the DMC is compromised. Any information that is needed by regulatory agencies would be available via interim reporting and the data collected and analyzed according to the protocol.

Section 5. DMCs and Regulatory Reporting Requirements

Section 5.1. Safety Reporting

On page 17, the guidance document states: "The sponsor may make the report with or without unblinding the case, as appropriate". AdvaMed suggests that FDA clarify the

circumstances when unblinding would be appropriate, or when not unblinding would be inappropriate.

Section 5.2. Expedited Development

On page 18, the guidance document states: "The sponsor should construct such procedures [for interactions between FDA and DMC] to maintain the integrity of the trial while providing flexibility for sharing of interim data in the unusual circumstance when such data are considered essential for regulatory decision-making". AdvaMed requests that FDA clarify how it believes this goal could be accomplished.

Section 6. Independence of the DMC

Section 6.3. Risks of Sponsor Exposure to Interim Comparative Data

The draft guidance suggests that blinding of data from the sponsor is so important that it recommends hiring independent statisticians to perform interim analyses. AdvaMed believes it is unwise to maintain total independence of statisticians in device trials. Hiring independent statisticians, external to the sponsor, will likely result in less reliable data, increased chance of misinterpreting data, and delayed submission of trial results. This guidance contains recommendations for preventing bias in study conduct and analysis. These recommendations can be incorporated into the sponsor's statistical analysis activities without hiring outside consultants. AdvaMed recommends that the agency clearly state that the use of independent statisticians is an option that a sponsor may consider. We maintain that it is the sponsor's responsibility to demonstrate that bias issues are adequately addressed in a clinical trial, with or without a DMC.

Section 6.4. Conduct of the Interim Analysis

In this section, FDA suggests "the integrity of the trial is best protected when the statistician preparing unblinded data for the DMC is external to the sponsor." AdvaMed believes that this implies too restrictive a role for an industry statistician, i.e., that the industry statistician should not be the one responsible for providing raw data analysis from the clinical trial to the DMC because of the potential to disclose the interim results to corporate management who then may be tempted to re-design the trial. AdvaMed maintains that industry statisticians should be viewed as professionals who can handle the dual role of keeper of interim data and employee of the company.

Advantages to having in-house statisticians include:

- Industry statistician's in-depth knowledge of the products under investigation
- Industry statistician's in-depth knowledge of possible clinical outcomes.
- Industry statisticians can provide better assessment of the quality of data and therefore, provide more effective response to data management issues.

Issues with independent statisticians include:

- The DMC loses the detailed knowledge the sponsor statistician has of the device/therapy area, the study methods, and the other data elements.
- Financial link between the independent statistician and the sponsor remains as the sponsor still pays the independent statistician.
- Limited supply and high demand of the external statisticians may result in delays in the completion of work and in important decisions or milestones.

AdvaMed again stresses the need for FDA to clearly state that industry statisticians are an acceptable option to the use of an external statistician.

AdvaMed is pleased to have the opportunity to submit comments on FDA's draft guidance.

Sincerely,

Janet Trunzo

Janet Trunzo
Vice President
Technology and Regulatory Affairs